Complete Summary

GUIDELINE TITLE

Referral guidelines for suspected cancer in adults and children.

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer in adults and children. London (UK): Royal College of General Practitioners; 2005 Jun. 791 p. [452 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Suspected cancer including:

- Lung cancer
- Upper gastrointestinal cancers
- Lower gastrointestinal cancers
- Breast cancer
- Gynaecological cancers
- Urological/renal cancers
- Haematological malignancies
- Skin cancers
- Head and neck including oral cancers
- Brain/central nervous system malignancies
- Sarcomas

- Children's and young people's malignancies

GUIDELINE CATEGORY

Diagnosis
Evaluation
Risk Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Health Care Providers
Patients
Physicians

GUIDELINE OBJECTIVE(S)

To offer advice on the referral of patients with suspected cancer to specialist services

Note: The guideline will not cover:

- The organisation or effectiveness of screening schemes for cancer
- The tests undertaken after referral, therefore definitive diagnosis will not be covered
- Referral for suspected recurrence or metastases in previously diagnosed cancer, or referral for palliative care

TARGET POPULATION

Patients in all age groups suspected of having one of the cancers covered by the guideline

Note: The guideline documentation and recommendations are limited to the detection of people who may have cancer in primary care, and do not address the assessment or investigation of patients after referral.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Consideration of the need for referral based on symptoms, signs and other factors, taking into account variation in risk by age and ethnic group
2. Performing initial investigations that contribute to the assessment of patients prior to, or in association with, urgent referral for suspected cancer
3. Assessing the need for urgent referral, and the consequences of delay in referral

4. Provision of information and support needs of patients who are referred for suspected cancer, and their families
5. Monitoring of patients after referral but before the first specialist assessment

MAJOR OUTCOMES CONSIDERED

- Signs and symptoms of cancer
- Predictive value of diagnostic tests
- Sensitivity and specificity of diagnostic tests
- Cost factors
- Time to referral
- Mortality

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The aim of the literature review was to seek to identify all available, relevant published evidence in relation to the key clinical questions generated by the guideline development group (GDG). The prioritised key clinical questions (KCQs) were turned into evidence-based questions (EBQs) by the project lead and systematic reviewer. Literature searches were conducted using generic search filters and modified filters, designed to best address the specific question being investigated. Searches included both medical subject headings (MeSH terms) and free-text terms. Details of all literature searches are available from the National Collaborating Centre for Primary Care (NCC-PC), University of Leicester and an example can be seen in Appendix D of the original guideline document.

The information librarian developed a search strategy for each question with the assistance of the systematic reviewer and the project lead. Searches were re-run at the end of the guideline development process, thus including evidence published up to the end of June 2004.

Depending on the clinical area, some or all of the following databases were searched: Cochrane Library (up to Issue 2, 2004) was searched to identify any relevant systematic reviews, and for reports of randomised controlled trials, MEDLINE (for the period January 1966 to June 2004, on the OVID interface), EMBASE (for the period January 1980 to June 2004, on the OVID interface), the Cumulative Index of Nursing and Allied Health Literature (for the period January 1982 to November 2003, on the Dialog DataStar interface), PsycINFO (for the period 1887 to June 2004, on the OVID and the Dialog DataStar interfaces), the Health Management Information Consortium database (HMIC), the British Nursing Index (BNI), and the Allied and Complementary Medicine Database (AMED). Searches for non-systematic reviews of the literature were limited to 1997 to June

2004. This was a pragmatic decision that draws on the search strategies used by the North Of England Evidence Based Guideline Development Project. No systematic attempt was made to search "grey literature" (such as conference proceedings, abstracts, unpublished reports or trials, etc.).

Existing systematic reviews and meta-analyses relating to referral for suspected cancer were identified. Recent (last six years) high quality reviews of referral for suspected cancer were also identified. New searches, including identification of relevant randomised controlled trials (RCTs), were conducted in areas of importance to the guideline development process, for which existing systematic reviews are unable to provide valid or up to date answers. The search strategy was dictated by the exact EBQ the GDG wished to answer. Expert knowledge of group members was also drawn upon to corroborate the search strategy.

The National Research Register (NRR), National Guidelines Clearinghouse (NGC), New Zealand Guidelines Group (NZGG), and the Guidelines International Network (GIN) were searched to identify any existing relevant guidelines produced by other organisations. The reference lists in these guidelines were checked against the methodology team's search results to identify any missing evidence.

The titles and abstracts of records retrieved by the searches were scanned for relevance to the GDG's clinical questions. Any potentially relevant publications were obtained in full text. These were assessed against the inclusion criteria and the reference lists were scanned for any articles not previously identified. Further references were also suggested by the GDG. Evidence submitted by stakeholder organisations that was relevant to the GDG's KCQs, and was of at least the same level of evidence as that identified by the literature searches, was also included.

Initial Review

The searches were first sifted by the information librarian and systematic reviewer to exclude papers that did not relate to the scope of the guideline. The abstracts of the remaining papers were scrutinised for relevance to the EBQ under consideration. Initially both the systematic reviewer and project lead reviewed the abstracts independently. This proved impractical as the guideline progressed and the task was delegated to the systematic reviewer. The project lead was asked to review the abstracts in cases of uncertainty.

The papers chosen for inclusion were obtained and were assessed for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differ according to study type and were based on the checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN). Critical appraisal was carried out by the systematic reviewer. Further appraisal was provided by the GDG members at the relevant GDG meeting.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia - Systematic review or meta-analysis of randomised controlled trials

Ib - At least one randomised controlled trial

IIa - At least one well-designed controlled study without randomization

IIb - At least one well-designed quasi-experimental study, such as a cohort study

III - Well-designed non-experimental descriptive studies, case-control studies, and case series

IV - Expert committee reports, opinions and/or clinical experience of respected authorities

NICE - National Institute for Health and Clinical Excellence (NICE) guidelines or Health Technology Appraisal programme

Levels of Evidence for Studies of the Accuracy of Diagnostic Tests

Ia - Systematic review (with homogeneity*) of level-1 studies**

Ib - Level-1 studies**

II - Level-2 studies***; Systematic reviews of level-2 studies

III - Level-3 studies****; Systematic reviews of level-3 studies

IV - Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research, or 'first principles'.

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

**Level-1 studies are studies that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

***Level-2 studies are studies that have only one of the following:

- Narrow population (the sample does not reflect the population to whom the test would apply)

- Use a poor reference standard (defined as that where a 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- The comparison between the test and reference standard is not blind
- Case-control studies

****Level-3 studies are studies that have at least two of three of the features listed above***

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The data were extracted to a standard template on an evidence table. The findings were summarised by the systematic reviewer into a series of evidence statements and an accompanying narrative review. The project lead independently assessed the accuracy of the derived evidence statements. None of the evidence-based questions (EBQs) required the preparation of a quantitative synthesis (meta-analysis) by the project team.

The evidence statements were graded by the project lead according to the established hierarchy of evidence table presented (see "Rating Scheme for the Strength of the Evidence" field). This system reflects the susceptibility to bias inherence in particular study designs.

The type of EBQ dictates the highest level of evidence that may be sought. For questions relating to therapy/treatment the highest possible level of evidence is a systematic review or meta-analysis of randomised controlled trials (RCTs) (evidence level Ia) or an individual RCT (evidence level Ib). For questions relating to prognosis, the highest possible level of evidence is a cohort study (evidence level IIb). For diagnostic tests, the highest possible level of evidence is a test evaluation study using a quasi-experimental design that uses a blind comparison of the test with a validated reference standard applied to a sample of patients who are representative of the population to whom the test would apply (evidence level IIb). For questions relating to information needs and support, the highest possible level of evidence is a descriptive study using either questionnaire survey or qualitative methods (III).

For each clinical question, the highest level of evidence was selected. If a systematic review, meta-analysis, or RCT existed in relation to an EBQ, studies of a weaker design were ignored.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the evidence tables (Appendices A and B of the original guideline document).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guideline development group (GDG) met at six weekly intervals for 18 months to review the evidence identified by the methodology team, to comment on its quality and completeness, and to develop recommendations for clinical practice based on the available evidence. The final recommendations were agreed by the GDG.

For each key clinical question (KCQ), the recommendations were derived from the evidence statements presented to the GDG. The link between the evidence statement and recommendation was made explicit. The GDG were able to reach their agreed recommendations through a process of informal consensus.

Each recommendation was graded according to the level of evidence upon which it was based using the established grading of recommendations presented in the section below titled "Rating Scheme for the Strength of the Recommendations." For questions relating to therapy/treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For questions relating to prognosis and diagnostic tests, the generally appropriate level of evidence (a cohort study) would equate to a grade B recommendation. For questions relating to information needs and support, the generally appropriate level of evidence (descriptive study) would equate to a grade C recommendation. It is important that the grading in such areas is not treated as inferior to those of therapy as it is based on the existence of relevant evidence.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

A - Based directly on level I evidence

B - Based directly on level II evidence or extrapolated from level I evidence

C - Based directly on level III evidence or extrapolated from level I or level II evidence

D - Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence

A (NICE) - Recommendation taken from National Institute for Health and Clinical Excellence (NICE) guideline or Technology Appraisal

GPP - Good practice points based on the clinical experience of the Guideline Development Group (GDG)

Classification of Recommendations for Studies of the Accuracy of Diagnostic Tests

A (DS) - Studies with level of evidence Ia or Ib

B (DS) - Studies with level of evidence II

C (DS) - Studies with level of evidence III

D (DS) - Based on studies with level of evidence IV

DS - Diagnostic studies

COST ANALYSIS

Health Economics

Identified titles and abstracts from the economics searches were reviewed by the health economist and full papers obtained as appropriate. The full papers were critically appraisal by the health economist using a standard validated checklist. A general descriptive overview of the studies, their qualities, and conclusions was presented and summarized in the form of a short narrative review. The economic evidence was not summarized in the form of meta-analyses given the limited evidence found.

The guideline development group (GDG) identified the economics of referral of people with suspected lower gastrointestinal cancer as an important area where further analysis was needed. This area was chosen because there is a high prevalence of the primary symptoms of bowel cancer in the community (rectal bleeding, changes in bowel habit and abdominal pain) relative to the low incidence of bowel cancer. The results of this analysis are presented in Appendix C of the original guideline document.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guideline was validated through two consultations.

1. The first draft of the guideline (The full guideline, National Institute for Health and Clinical Excellence (NICE) guideline and Quick Reference Guide) were consulted with Stakeholders and comments were considered by the Guideline Development Group (GDG)
2. The final consultation draft of the Full guideline, the NICE guideline, and the Information for the Public were submitted to stakeholders for final comments.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence (Ia-IV) and grades of recommendations (A-D, A [NICE], and GPP) are defined at the end of the "Major Recommendations" field.

Support and Information Needs of People with Suspected Cancer at the Time of Referral

D - Patients should be able to consult a primary healthcare professional of the same sex if preferred.

D - Primary healthcare professionals should discuss with patients (and carers as appropriate, taking account of the need for confidentiality) their preferences for being involved in decision-making about referral options and further investigations (including their potential risks and benefits), and ensure they have the time for this.

D - When cancer is suspected in a child, the referral decision and information to be given to the child should be discussed with the parents or carers (and the patient if appropriate)

D - Adult patients who are being referred with suspected cancer should normally be told by the primary healthcare professional that they are being referred to a cancer service, but if appropriate they should be reassured that most people referred will not have a diagnosis of cancer, and alternative diagnoses should be discussed.

D - Primary healthcare professionals should be willing and able to give the patient information on the possible diagnosis (both benign and malignant) in accordance with the patient's wishes for information. Current advice on communicating with patients and/or their carers and breaking bad news* should be followed.

> *Note: Improving communication between doctors and patients. A report of the working party of the Royal College of Physicians (1997) www.rcplondon.ac.uk/pubs/brochures/pub_print_icbdp.htm

D - The information given to patients, family, and/or carers as appropriate by the primary healthcare professional should cover, among other issues:

- Where patients are being referred to
- How long they will have to wait for the appointment
- How to obtain further information about the type of cancer suspected or help prior to the specialist appointment
- Who they will be seen by
- What to expect from the service the patient will be attending
- What type of tests will be carried out, and what will happen during diagnostic procedures
- How long it will take to get a diagnosis or test results
- Whether they can take someone with them to the appointment
- Other sources of support, including those for minority groups

D - When referring a patient with suspected cancer to a specialist service, primary healthcare professionals should assess the patient's need for continuing support

while waiting for their referral appointment. This should include inviting the patient to contact the primary healthcare professional again if they have more concerns or questions before they see a specialist.

D - Consideration should be given by the primary healthcare professional to meeting the information and support needs of parents and carers. Consideration should also be given to meeting these particular needs for the people for whom they care, such as children and young people, and people with special needs (for instance, people with learning disabilities or sensory impairment).

D - The primary healthcare professional should be aware that some patients find being referred for suspected cancer particularly difficult because of their personal circumstances, such as age, family or work responsibilities, isolation, or other health or social issues.

D - Primary healthcare professionals should provide culturally appropriate care, recognising the potential for different cultural meanings associated with the possibility of cancer, the relative importance of family decision-making and possible unfamiliarity with the concept of support outside the family.

D - The primary healthcare professional should be aware that men may have similar support needs to women but may be more reticent about using support services.

D - If the patient has additional support needs because of their personal circumstances, the specialist should be informed (with the patient's agreement).

D - All members of the primary healthcare team should have available to them information in a variety of formats on both local and national sources of additional support for patients who are being referred with suspected cancer.

D - In situations where diagnosis or referral has been delayed, or there is significant compromise of the doctor/patient relationship, the primary healthcare professional should take care to assess the information and support needs of the patient, parents, and carers, and make sure these needs are met. The patient should be given the opportunity to consult another primary healthcare professional if they wish.

D - Primary healthcare professionals should promote awareness of key presenting features of cancer when appropriate.

<u>The Diagnostic Process</u>

D - Diagnosis of any cancer on clinical grounds alone can be difficult. Primary healthcare professionals should be familiar with the typical presenting features of cancers, and be able to readily identify these features when patients consult with them.

D - Cancers usually present with symptoms commonly associated with benign conditions. The primary healthcare professional should be ready to review the

initial diagnosis in patients in whom common symptoms do not resolve as expected.

D - Primary healthcare professionals must be alert to the possibility of cancer when confronted by unusual symptom patterns or when patients thought not to have cancer fail to recover as expected. In such circumstances, the primary healthcare professional should systematically review the patient's history and examination, and refer urgently if cancer is a possibility.

D - Cancer is uncommon in children, and its detection can present particular difficulties. Primary healthcare professionals should recognise that parents are usually the best observers of their children, and should listen carefully to their concerns. Primary healthcare professionals should also be willing to reassess the initial diagnosis or to seek a second opinion from a colleague if a child fails to recover as expected.

C - Primary healthcare professionals should take part in continuing education, peer review, and other activities to improve and maintain their clinical consulting, reasoning, and diagnostic skills, in order to identify at an early stage, patients who may have cancer, and to communicate the possibility of cancer to the patient.

D - Discussion with a specialist should be considered if there is uncertainty about the interpretation of symptoms and signs, and whether a referral is needed. This may also enable the primary healthcare professional to communicate their concerns and a sense of urgency to secondary healthcare professionals when symptoms are not classical (for example, by telephone or e-mail).

D - There should be local arrangements in place to ensure that letters about non-urgent referrals are assessed by the specialist, the patient being seen more urgently if necessary.

D - There should be local arrangements in place to ensure a maximum waiting period for non-urgent referrals, in accordance with national targets and local arrangements.

D - There should be local arrangements in place to identify those patients who miss their appointments so that they can be followed up.

D - The primary healthcare professional should include all appropriate information in referral correspondence, including whether the referral is urgent or non-urgent.

D - The primary healthcare professional should use local referral proformas if these are in use.

D - Once the decision to refer has been made, the primary healthcare professional should make sure that the referral is made within 1 working day.

D - A patient who presents with symptoms suggestive of cancer should be referred by the primary healthcare professional to a team specialising in the management of the particular type of cancer, depending on local arrangements.

D - In patients with features typical of cancer, investigations in primary care should not be allowed to delay referral. In patients with less typical symptoms and signs that might, nevertheless, be due to cancer, investigations may be necessary, but should be undertaken urgently to avoid delay. If specific investigations are not readily available locally, an urgent specialist referral should be made.

Lung Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of lung cancer should be referred to a team specialising in the management of lung cancer, depending on local arrangements.

Specific Recommendations

D - An urgent referral for a chest x-ray should be made when a patient presents with:

- Haemoptysis, or
- Any of the following unexplained persistent (that is, lasting more than 3 weeks) symptoms and signs:
    - Chest and/or shoulder pain
    - Dyspnoea
    - Weight loss
    - Chest signs
    - Hoarseness
    - Finger clubbing
    - Cervical and/or supraclavicular lymphadenopathy
    - Cough with or without any of the above
    - Features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver, or skin)

  A report should be made back to the referring primary healthcare professional within 5 days of referral.

D - An urgent referral should be made for any of the following:

- Persistent haemoptysis in smokers or ex-smokers who are aged 40 years and older
- A chest x-ray suggestive of lung cancer (including pleural effusion and slowly resolving consolidation)

C - Immediate referral should be considered for the following:

- Signs of superior vena caval obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)
- Stridor

Risk Factors

C - Patients in the following categories have a higher risk of developing lung cancer:

- Are current or ex-smokers
- Have smoking-related chronic obstructive pulmonary disease (COPD)
- Have been exposed to asbestos
- Have had a previous history of cancer (especially head and neck)

An urgent referral for a chest x-ray or to a team specialising in the management of lung cancer should be made as for other patients but may be considered sooner, for example if symptoms or signs have lasted for less than 3 weeks.

Investigations

D - Unexplained changes in existing symptoms in patients with underlying chronic respiratory problems should prompt an urgent referral for chest x-ray.

D - If the chest x-ray is normal, but there is a high suspicion of lung cancer, patients should be offered an urgent referral.

C - In individuals with a history of asbestos exposure and recent onset of chest pain, shortness of breath, or unexplained systemic symptoms, lung cancer should be considered and a chest x-ray arranged. If this indicates a pleural effusion, pleural mass, or any suspicious lung pathology, an urgent referral should be made.

Upper Gastrointestinal Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of upper gastrointestinal cancer should be referred to a team specialising in the management of upper gastrointestinal cancer, depending on local arrangements.

Specific Recommendations

C - An urgent referral for endoscopy or to a specialist with expertise in upper gastrointestinal cancer should be made for patients of any age with dyspepsia* who present with any of the following:

- Chronic gastrointestinal bleeding
- Dysphagia
- Progressive unintentional weight loss
- Persistent vomiting
- Iron deficiency anaemia
- Epigastric mass
- Suspicious barium meal

*Note: The definition of dyspepsia is taken from the NICE guideline on dyspepsia (see National Guideline Clearinghouse [NGC] summary of the NICE guideline

Dyspepsia: managing dyspepsia in adults in primary care). Dyspepsia in unselected patients in primary care is defined broadly to include patients with recurrent epigastric pain, heartburn or acid regurgitation, with or without bloating, nausea, or vomiting.

D - In patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, an urgent referral for endoscopy should be made.

D - In patients aged less than 55 years, endoscopic investigation of dyspepsia is not necessary in the absence of alarm symptoms.

C - In patients presenting with dysphagia (interference with the swallowing mechanism that occurs within 5 seconds of having commenced the swallowing process), an urgent referral should be made.

C - Helicobacter pylori status should not affect the decision to refer for suspected cancer.

C - In patients without dyspepsia, but with unexplained weight loss or iron deficiency anaemia, the possibility of upper gastrointestinal cancer should be recognised and an urgent referral for further investigation considered.

C - In patients with persistent vomiting and weight loss in the absence of dyspepsia, upper gastro-oesophageal cancer should be considered and, if appropriate, an urgent referral should be made.

C - An urgent referral should be made for patients presenting with either:

- Unexplained upper abdominal pain and weight loss, with or without back pain, or
- An upper abdominal mass without dyspepsia

C - In patients with obstructive jaundice an urgent referral should be made, depending on the patient's clinical state. An urgent ultrasound investigation may be considered if available.

Risk Factors

C - In patients with unexplained worsening of their dyspepsia, an urgent referral should be considered if they have any of the following known risk factors:

- Barrett's oesophagus
- Known dysplasia, atrophic gastritis, or intestinal metaplasia
- Peptic ulcer surgery more than 20 years ago

Investigations

C - Patients being referred urgently for endoscopy should ideally be free from acid suppression medication, including proton pump inhibitors or H_2 receptor antagonists, for a minimum of 2 weeks.

D - In patients where the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be carried out in accordance with local arrangements.

D - All patients with new onset dyspepsia should be considered for a full blood count in order to detect iron deficiency anaemia.

Lower Gastrointestinal Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of colorectal or anal cancer should be referred to a team specialising in the management of lower gastrointestinal cancer, depending on local arrangements.

D - In patients with equivocal symptoms who are not unduly anxious, it is reasonable to use a period of "treat, watch, and wait" as a method of management.

C - In patients with unexplained symptoms related to the lower gastrointestinal tract, a digital rectal examination should always be carried out, provided this is acceptable to the patient.

Specific Recommendations

C - In patients aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for 6 weeks or more, an urgent referral should be made.

C - In patients aged 60 years and older, with rectal bleeding persisting for 6 weeks or more without a change in bowel habit and without anal symptoms, an urgent referral should be made.

C - In patients aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or more without rectal bleeding, an urgent referral should be made.

C - In patients presenting with a right lower abdominal mass consistent with involvement of the large bowel, an urgent referral should be made, irrespective of age.

C - In patients presenting with a palpable rectal mass (intraluminal and not pelvic), an urgent referral should be made, irrespective of age. (A pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist.)

C - In men of any age with unexplained* iron deficiency anaemia and a haemoglobin of 11 g/100 mL or below, an urgent referral should be made.

C - In non-menstruating women with unexplained* iron deficiency anaemia and a haemoglobin of 10 g/100 mL or below, an urgent referral should be made.

*Note: "Unexplained" in this context means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (for example, non-steroidal anti-inflammatory drug treatment or blood dyscrasia).

Risk Factors

C - In patients with ulcerative colitis or a history of ulcerative colitis, a plan for follow-up should be agreed with a specialist and offered to the patient as a normal procedure in an effort to detect colorectal cancer in this high-risk group.

C - There is insufficient evidence to suggest that a positive family history of colorectal cancer can be used as a criterion to assist in the decision about referral of a symptomatic patient.

Investigations

C (DS) - In patients with equivocal symptoms, a full blood count may help in identifying the possibility of colorectal cancer by demonstrating iron deficiency anaemia, which should then determine if a referral should be made and its urgency.

D - In patients for whom the decision to refer has been made, a full blood count may assist specialist assessment in the outpatient clinic. This should be in accordance with local arrangements.

D - In patients for whom the decision to refer has been made, no examinations or investigations other than those referred to earlier (abdominal and rectal examination, full blood count) are recommended as this may delay referral.

Breast Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of breast cancer should be referred to a team specialising in the management of breast cancer.

C - In most cases, the definitive diagnosis will not be known at the time of referral, and many patients who are referred will be found not to have cancer. However, primary healthcare professionals should convey optimism about the effectiveness of treatment and survival because a patient being referred with a breast lump will be naturally concerned.

D - People of all ages who suspect they have breast cancer may have particular information and support needs. The primary healthcare professional should discuss these needs with the patient and respond sensitively to them.

D - Primary healthcare professionals should encourage all patients, including women over 50 years old, to be breast aware* in order to minimise delay in the presentation of symptoms.

*Note: Breast awareness means knowing what your breasts look and feel like normally. Evidence suggests that there is no need to follow a specific or detailed routine such as Breast Self Examination, but women should be aware of any changes in their breasts.

Specific Recommendations

C - A woman's first suspicion that she may have breast cancer is often when she finds a lump in her breast. The primary healthcare professional should examine the lump with the patient's consent. The features of a lump that should make the primary healthcare professional strongly suspect cancer are a discrete, hard lump with fixation, with or without skin tethering. In patients presenting in this way an urgent referral should be made, irrespective of age.

C - In a woman aged 30 years and older with a discrete lump that persists after her next period, or presents after menopause, an urgent referral should be made.

C/D - Breast cancer in women aged younger than 30 years is rare, but does occur. Benign lumps (for example, fibroadenoma) are common, however, and a policy of referring these women urgently would not be appropriate; instead, non-urgent referral should be considered. However, in women aged younger than 30 years with:

- C - a lump that enlarges, or
- C - a lump that has other features associated with cancer (fixed and hard), or
- D - in whom there are other reasons for concern such as family history

An urgent referral should be made.

D - The patient's history should always be taken into account. For example, it may be appropriate, in discussion with a specialist, to agree referral within a few days in patients reporting a lump or other symptom that has been present for several months.

C - In a patient who has previously had histologically confirmed breast cancer, who presents with a further lump or suspicious symptoms, an urgent referral should be made, irrespective of age.

C - In patients presenting with unilateral eczematous skin or nipple change that does not respond to topical treatment, or with nipple distortion of recent onset, an urgent referral should be made.

C - In patients presenting with spontaneous unilateral bloody nipple discharge, an urgent referral should be made.

C - Breast cancer in men is rare and is particularly rare in men under 50 years of age. However, in a man aged 50 years and older with a unilateral, firm subareaolar mass with or without nipple distortion or associated skin changes, an urgent referral should be made.

Investigations

D - In patients presenting with symptoms and/or signs suggestive of breast cancer, investigation prior to referral is not recommended.

B (DS) - In patients presenting solely with breast pain, with no palpable abnormality, there is no evidence to support the use of mammography as a discriminatory investigation for breast cancer. Therefore, its use in this group of patients is not recommended. Non-urgent referral may be considered in the event of failure of initial treatment and/or unexplained persistent symptoms.

Gynaecological Cancer

General Recommendations

D - A patient who presents with symptoms suggesting gynaecological cancer should be referred to a team specialising in the management of gynaecological cancer, depending on local arrangements.

Specific Recommendations

C - The first symptoms of gynaecological cancer may be alterations in the menstrual cycle, intermenstrual bleeding, postcoital bleeding, postmenopausal bleeding, or vaginal discharge. For a patient who presents with any of these symptoms, the primary healthcare professional should undertake a full pelvic examination, including speculum examination of the cervix.

C - In patients found on examination of the cervix to have clinical features that raise the suspicion of cervical cancer, an urgent referral should be made. A cervical smear test is not required before referral, and a previous negative cervical smear result is not a reason to delay referral.

D - Ovarian cancer is particularly difficult to diagnose on clinical grounds as the presentation may be with vague, non-specific abdominal symptoms alone (bloating, constipation, abdominal or back pain, urinary symptoms). In a woman presenting with any unexplained abdominal or urinary symptoms, abdominal palpation should be carried out. If there is significant concern, a pelvic examination should be considered if appropriate and acceptable to the patient.

C - Any woman with a palpable abdominal or pelvic mass on examination that is not obviously uterine fibroids or not of gastrointestinal or urological origin should have an urgent ultrasound scan. If the scan is suggestive of cancer, or if ultrasound is not available, an urgent referral should be made.

C - When a woman who is not on hormone replacement therapy presents with postmenopausal bleeding, an urgent referral should be made.

C - When a woman on hormone replacement therapy presents with persistent or unexplained postmenopausal bleeding after cessation of hormone replacement therapy for 6 weeks, an urgent referral should be made.

C - Tamoxifen can increase the risk of endometrial cancer. When a woman taking tamoxifen presents with postmenopausal bleeding, an urgent referral should be made.

D - An urgent referral should be considered in a patient with persistent intermenstrual bleeding and a negative pelvic examination.

Vulvar Cancer

C - When a woman presents with vulval symptoms, a vulval examination should be offered. If an unexplained vulval lump is found, an urgent referral should be made.

D - Vulval cancer can also present with vulval bleeding due to ulceration. A patient with these features should be referred urgently.

C - Vulval cancer may also present with pruritus or pain. For a patient who presents with these symptoms, it is reasonable to use a period of "treat, watch, and wait" as a method of management. But this should include active follow-up until symptoms resolve or a diagnosis is confirmed. If symptoms persist, the referral may be urgent or non-urgent, depending on the symptoms and the degree of concern about cancer.

Urological Cancers

General Recommendations

D - A patient who presents with symptoms or signs suggestive of a urological cancer should be referred to a team specialising in the management of urological cancers, depending on local arrangements.

Specific Recommendations

Prostate Cancer

C - Patients presenting with symptoms suggesting prostate cancer should have a digital rectal examination (DRE) and prostate specific antigen (PSA) test after counselling. Symptoms will be related to the lower urinary tract and may be inflammatory or obstructive.

C - Prostate cancer is also a possibility in male patients with any of the following unexplained symptoms:

- Erectile dysfunction
- Haematuria
- Lower back pain
- Bone pain
- Weight loss, especially in the elderly

These patients should also be offered a DRE and a PSA test.

C - Urinary infection should be excluded before PSA testing, especially in men presenting with lower tract symptoms. The PSA test should be postponed for at least 1 month after treatment of a proven urinary infection.

C - If a hard, irregular prostate typical of a prostate carcinoma is felt on rectal examination, then the patient should be referred urgently. The PSA should be measured and the result should accompany the referral. Patients do not need urgent referral if the prostate is simply enlarged and the PSA is in the age-specific reference range*.

> *Note: The age-specific cut-off PSA measurements recommended by the Prostate Cancer Risk Management Programme are as follows: aged 50 to 59 years $\geq$3.0 ng/mL; aged 60 to 69 years $\geq$4.0 ng/mL; aged 70 years and older $\geq$5.0 ng/mL. (Note that there are no age-specific reference ranges for men aged over 80 years. Nearly all men of this age have at least a focus of cancer in the prostate. Prostate cancer only needs to be diagnosed in this age group if it is likely to need palliative treatment).

C - In a male a patient with or without lower urinary tract symptoms and in whom the prostate is normal on DRE but the age-specific PSA is raised or rising, an urgent referral should be made. In those patients whose clinical state is compromised by other comorbidities, a discussion with the patient or carers and/or a specialist in urological cancer may be more appropriate.

C - Symptomatic patients with high PSA levels should be referred urgently.

D - If there is doubt about whether to refer an asymptomatic male with a borderline level of PSA, the PSA test should be repeated after an interval of 1 to 3 months. If the second test indicates that the PSA level is rising, the patient should be referred urgently.

Bladder and Renal Cancers

C - Male or female adult patients of any age who present with painless macroscopic haematuria should be referred urgently.

D - In male or female patients with symptoms suggestive of a urinary infection who also present with macroscopic haematuria, investigations should be undertaken to diagnose and treat the infection before consideration of referral. If infection is not confirmed the patient should be referred urgently.

C - In all adult patients aged 40 years and older who present with recurrent or persistent urinary tract infection associated with haematuria, an urgent referral should be made.

C - In patients under 50 years of age with microscopic haematuria, the urine should be tested for proteinuria and serum creatinine levels measured. Those with proteinurea or raised serum creatinine should be referred to a renal physician. If there is no proteinuria and serum creatinine is normal, a non-urgent referral to a urologist should be made.

C - In patients aged 50 years and older who are found to have unexplained microscopic haematuria, an urgent referral should be made.

C - Any patient with an abdominal mass identified clinically or on imaging that is thought to be arising from the urinary tract should be referred urgently.

Testicular Cancer

C - Any patient with a swelling or mass in the body of the testis should be referred urgently.

D - An urgent ultrasound should be considered in men with a scrotal mass that does not transilluminate and/or when the body of the testis cannot be distinguished.

Penile Cancer

D - An urgent referral should be made for any patient presenting with symptoms or signs of penile cancer. These include progressive ulceration or a mass in the glans or prepuce particularly, but can involve the skin of the penile shaft. Lumps within the corpora cavernosa not involving penile skin are usually not cancer but indicate Peyronie's disease, which does not require urgent referral.

Haematological Cancers

General Recommendations

D - A patient who presents with symptoms suggesting haematological cancer should be referred to a team specialising in the management of haematological cancer, depending on local arrangements.

D - Primary healthcare professionals should be aware that haematological cancers can present with a variety of symptoms that may have a number of different clinical explanations.

C - Combinations of the following symptoms and signs may suggest haematological cancer and warrant full examination, further investigation (including a blood count and film), and possible referral:

- Fatigue
- Drenching night sweats
- Fever
- Weight loss
- Generalised itching
- Breathlessness
- Bruising
- Bleeding
- Recurrent infections
- Bone pain
- Alcohol-induced pain
- Abdominal pain

- Lymphadenopathy
- Splenomegaly

The urgency of referral depends on the severity of the symptoms and signs, and findings of investigations.

Specific Recommendations

D - In patients with a blood count or blood film reported as acute leukaemia, an immediate referral should be made.

C - In patients with persistent unexplained splenomegaly, an urgent referral should be made.

Investigations

B (DS) - Investigation of patients with persistent unexplained fatigue should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy), and repeated at least once if the patient's condition remains unexplained and does not improve.

B (DS) - Investigation of patients with unexplained lymphadenopathy should include a full blood count, blood film and erythrocyte sedimentation rate, plasma viscosity or C-reactive protein (according to local policy).

C (DS) - Any of the following additional features of lymphadenopathy should trigger further investigation and/or referral:

- Persistence for 6 weeks or more
- Lymph nodes increasing in size
- Lymph nodes greater than 2 cm in size
- Widespread nature
- Associated splenomegaly, night sweats, or weight loss

B (DS) - Investigation of a patient with unexplained bruising, bleeding, and purpura or symptoms suggesting anaemia should include a full blood count, blood film, clotting screen and erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein (according to local policy).

C (DS) - A patient with bone pain that is persistent and unexplained should be investigated with full blood count and x-ray, urea and electrolytes, liver and bone profile, PSA test (in males) and erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein (according to local policy).

C - In patients with spinal cord compression or renal failure suspected of being caused by myeloma, an immediate referral should be made.

Skin Cancer

D - A patient presenting with skin lesions suggestive of skin cancer or in whom a biopsy has been confirmed should be referred to a team specialising in skin cancer.

C - All primary healthcare professionals should be aware of the 7-point weighted checklist (see recommendation below regarding 7-point checklist under "Specific Recommendations" for "Melanoma") for assessment of pigmented skin lesions.

D - All primary healthcare professionals who perform minor surgery should have received appropriate accredited training in relevant aspects of skin surgery including cryotherapy, curettage, and incisional and excisional biopsy techniques, and should undertake appropriate continuing professional development.

D - Patients with persistent or slowly evolving unresponsive skin conditions in which the diagnosis is uncertain and cancer is a possibility should be referred to a dermatologist.

C (DS) - All excised skin specimens should be sent for pathological examination.

D - On making a referral of a patient in whom an excised lesion has been diagnosed as malignant, a copy of the pathology report should be sent with the referral correspondence, as there may be details (such as tumour thickness, excision margin) that will specifically influence future management.

Specific Recommendations

Melanoma

D - Change is a key element in diagnosing malignant melanoma. For low-suspicion lesions, careful monitoring for change should be undertaken using the 7-point checklist (see recommendation below) for 8 weeks. Measurement should be made with photographs and a marker scale and/or ruler.

C - All primary healthcare professionals should use the weighted 7-point checklist in the assessment of pigmented lesions to determine referral:

Major features of the lesions:

- Change in size
- Irregular shape
- Irregular colour

Minor features of the lesions:

- Largest diameter 7 mm or more
- Inflammation
- Oozing
- Change in sensation

Suspicion is greater for lesions scoring 3 points or more (based on major features scoring 2 points each and minor features scoring 1 point each). However, if there

are strong concerns about cancer, any one feature is adequate to prompt urgent referral.

C - In patients with a lesion suspected to be melanoma (see recommendation above regarding 7-point checklist under "Specific Recommendations" for "Melanoma"), an urgent referral to a dermatologist or other suitable specialist with experience of melanoma diagnosis should be made, and excision in primary care should be avoided.

Squamous Cell Carcinomas

C - Squamous cell carcinomas present as keratinizing or crusted tumours that may ulcerate. Non-healing lesions larger than 1 cm with significant induration on palpation, commonly on face, scalp, or back of hand with a documented expansion over 8 weeks, may be squamous cell carcinomas and an urgent referral should be made.

C - Squamous cell carcinomas are common in patients on immunosuppressive treatment, but may be atypical and aggressive. In patients who have had an organ transplant who develop new or growing cutaneous lesions, an urgent referral should be made.

C - In any patient with histological diagnosis of a squamous cell carcinoma made in primary care, an urgent referral should be made.

Basal Cell Carcinomas

C - Basal cell carcinomas are slow growing, usually without significant expansion over 2 months, and usually occur on the face. Where there is a suspicion that the patient has a basal cell carcinoma, a nonurgent referral should be made.

Investigations

B (DS) - All pigmented lesions that are not viewed as suspicious of melanoma but are excised should have a lateral excision margin of 2 mm of clinically normal skin and cut to include subcutaneous fat in depth.

Head and Neck Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements.

D - Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after 6 weeks, an urgent referral should be made.

D - Primary healthcare professionals should advise all patients, including those with dentures, to have regular dental checkups.

Specific Recommendations

C - A patient who presents with unexplained red and white patches (including suspected lichen planus) of the oral mucosa that are:

- Painful, or
- Swollen, or
- Bleeding

An urgent referral should be made. A non-urgent referral should be made in the absence of these features. If oral lichen planus is confirmed, the patient should be monitored for oral cancer as part of routine dental examination.*

> *Note: See National Guideline Clearinghouse (NGC) summary of NICE guideline Dental recall: recall interval between routine dental examinations.

C - In patients with unexplained ulceration of the oral mucosa or mass persisting for more than 3 weeks, an urgent referral should be made.

C - In adult patients with unexplained tooth mobility persisting for more than 3 weeks, an urgent referral to a dentist should be made.

C - In any patient with hoarseness persisting for more than 3 weeks, particularly smokers aged 50 years and older and heavy drinkers, an urgent referral for a chest x-ray should be made. Patients with positive findings should be referred urgently to a team specialising in the management of lung cancer. Patients with a negative finding should be urgently referred to a team specialising in head and neck cancer.

C - In patients with an unexplained lump in the neck which has recently appeared or a lump which has not been diagnosed before that has changed over a period of 3 to 6 weeks, an urgent referral should be made.

D - In patients with an unexplained persistent swelling in the parotid or submandibular gland, an urgent referral should be made.

D - In patients with unexplained persistent sore or painful throat, an urgent referral should be made.

D - In patients with unilateral unexplained pain in the head and neck area for more than 4 weeks, associated with otalgia (ear ache) but with normal otoscopy, an urgent referral should be made.

Investigations

D - With the exception of persistent hoarseness (see recommendation above regarding hoarseness), investigations for head and neck cancer in primary care are not recommended as they can delay referral.

Thyroid Cancers

D - In patients presenting with symptoms of tracheal compression including stridor due to thyroid swelling, immediate referral should be made.

D - In patients presenting with a thyroid swelling associated with any of the following, an urgent referral should be made:

- A solitary nodule increasing in size
- A history of neck irradiation
- A family history of an endocrine tumour
- Unexplained hoarseness or voice changes
- Cervical lymphadenopathy
- Very young (pre-pubertal) patients
- Patients aged 65 years and older

D - In patients with a thyroid swelling without stridor or any of the features indicated in the recommendation above, the primary healthcare professional should request thyroid function tests. Patients with hyper- or hypothyroidism and an associated goitre are very unlikely to have thyroid cancer and could be referred, non-urgently, to an endocrinologist. Those with goitre and normal thyroid function tests who do not have any of the features indicated in the recommendation above should be referred non-urgently.

D - Initiation of other investigations by the primary healthcare professional, such as ultrasonography or isotope scanning, is likely to result in unnecessary delay and is not recommended.

Brain and Central Nervous System (CNS) Cancer

General Recommendations

D - A patient who presents with symptoms suggestive of brain or CNS cancer should be referred to an appropriate specialist, depending on local arrangements.

D - If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with a local specialist should be considered. If rapid access to scanning is available, this investigation should also be considered as an alternative.

Specific Recommendations

D - In patients with new, unexplained headaches or neurological symptoms, the primary healthcare professional should undertake a neurological examination guided by the symptoms, but including examination for papilloedema. The absence of papilloedema does not exclude the possibility of a brain tumour.

C - In any patient with symptoms related to the CNS (including progressive neurological deficit, new onset seizures, headaches, mental changes, cranial nerve palsy, unilateral sensorineural deafness) in whom a brain tumour is suspected, an urgent referral should be made. The development of new signs related to the CNS should be considered as potential indications for referral.

Headaches

C - In patients with headaches of recent onset accompanied by either features suggestive of raised intra-cranial pressure (for example, vomiting, drowsiness, postural related headache, headache with pulse synchronous tinnitus) or other focal or non-focal neurological symptoms (for example, blackout, change in personality or memory), an urgent referral should be made.

D - In patients with unexplained headaches of recent onset, present for at least 1 month but not accompanied by features suggestive of raised intracranial pressure (see recommendation above), discussion with a local specialist or referral (usually non-urgent) should be considered.

C - In patients with a new, qualitatively different unexplained headache that becomes progressively severe, an urgent referral should be made.

D - Re-assessment and re-examination is required if the patient does not progress according to expectations.

Seizures

C - A detailed history should be taken from the patient and an eyewitness to the event if possible, to determine whether or not a seizure is likely to have occurred*.

> *Note: See National Guideline Clearinghouse (NGC) summary of NICE guideline: The diagnosis and management of the epilepsies in adults and children in primary and secondary care.

C - In patients presenting with a seizure, a physical examination (including cardiac, neurological, mental state) and developmental assessment, where appropriate, should be carried out.

C - In any patient with suspected recent onset seizures, an urgent referral to a neurologist should be made.

Other Neurological Features

B/C/D - In patients with rapid progression of:

- B - Subacute focal neurological deficit
- C - Unexplained cognitive impairment, behavioural disturbance, or slowness or a combination of these

- D - Personality changes confirmed by a witness (for example, a carer, friend, or a family member) and for which there is no reasonable explanation even in the absence of the other symptoms and signs of a brain tumour

An urgent referral to an appropriate specialist should be considered.

Risk Factors

C - In patients previously diagnosed with any cancer an urgent referral should be made if the patient develops any of the following symptoms:

- Recent onset seizure
- Progressive neurological deficit
- Persistent headaches
- New mental or cognitive changes
- New neurological signs

Bone Cancer and Sarcoma

General Recommendations

D - A patient who presents with symptoms suggesting bone cancer or sarcoma should be referred to a team specialising in the management of bone cancer and sarcoma, or to a recognised bone cancer centre, depending on local arrangements.

D - If a primary healthcare professional has concerns about the interpretation of a patient's symptoms and/or signs, a discussion with the local specialist should be considered.

C (DS) - Patients with increasing, unexplained, or persistent bone pain or tenderness, particularly pain at rest (and especially if not in the joint), or an unexplained limp should be investigated by the primary healthcare professional urgently. The nature of the investigations will vary according to the patient's age and clinical features.

- In older people metastases, myeloma, or lymphoma, as well as sarcoma, should be considered.

Specific Recommendations

Bone Tumours

B (DS) - A patient with a suspected spontaneous fracture should be referred for an immediate x-ray.

C (DS) - If an x-ray indicates that bone cancer is a possibility, an urgent referral should be made. If the x-ray is normal but symptoms persist, the patient should be followed up and/or a repeat x-ray or bone function tests or a referral requested.

C (DS) - If the x-ray is normal but symptoms persist, the patient should be followed up and/or a repeat x-ray or bone function tests or a referral requested.

Soft Tissue Sarcomas

C - In patients presenting with a palpable lump, an urgent referral for suspicion of soft tissue sarcoma should be made if the lump is:

- Greater than about 5 cm in diameter
- Deep to fascia, fixed or immobile
- Painful
- Increasing in size
- A recurrence after previous excision

If there is any doubt about the need for referral, discussion with a local specialist should be undertaken.

C - If a patient has human immunodeficiency virus (HIV) disease, Kaposi's sarcoma should be considered and a referral made if this is suspected.

Children's Cancer

General Recommendations

D - Children and young people who present with symptoms and signs of cancer should be referred to a paediatrician or a specialist children's cancer service, if appropriate.

D - Childhood cancer is rare and may present initially with symptoms and signs associated with common conditions. Therefore, in the case of a child or young person presenting several times (for example, three or more times) with the same problem, but with no clear diagnosis, urgent referral should be made.

D - The parent is usually the best observer of the child's or young person's symptoms. The primary healthcare professional should take note of parental insight and knowledge when considering urgent referral.

D - Persistent parental anxiety should be a sufficient reason for referral of a child or young person, even when the primary healthcare professional considers that the symptoms are most likely to have a benign cause.

C - Persistent back pain in a child or young person can be a symptom of cancer and is indication for an examination, investigation with a full blood count and blood film, and consideration of referral.

D - There are associations between Down syndrome and leukaemia, neurofibromatosis and CNS tumours, and between other rare syndromes and some cancers. The primary healthcare professional should be alert to the potential significance of unexplained symptoms in children or young people with such syndromes.

D - The primary healthcare professional should convey information to the parents and child/young person about the reason for referral and which service the child/young person is being referred to so that they know what to do and what will happen next.

D - The primary healthcare professional should establish good communication with the parents and child/young person in order to develop the supportive relationship that will be required during the further management if the child/young person is found to have cancer.

Specific Recommendations

Leukaemia (Children of All Ages)

C (DS) - Leukaemia usually presents with a relatively short history of weeks rather than months. The presence of one or more of the following symptoms and signs requires investigation with full blood count and blood film:

- Pallor
- Fatigue
- Unexplained irritability
- Unexplained fever
- Persistent or recurrent upper respiratory tract infections
- Generalised lymphadenopathy
- Persistent or unexplained bone pain
- Unexplained bruising

If the blood film or full blood count indicates leukaemia then an urgent referral should be made.

C - The presence of either of the following signs in a child or young person requires immediate referral:

- Unexplained petechiae
- Hepatosplenomegaly

Lymphomas

Hodgkin's lymphoma presents typically with non tender cervical and/or supraclavicular lymphadenopathy. Lymphadenopathy can also present at other sites. The natural history is long (months). Only a minority of patients have systemic symptoms (itching, night sweats, fever).

Non Hodgkin's lymphoma typically shows a more rapid progression of symptoms, and may present with lymphadenopathy, breathlessness, superior vena cava (SVC) obstruction, abdominal distension.

C - Lymphadenopathy is more frequently benign in younger children but urgent referral is advised if one or more of the following characteristics are present, particularly if there is no evidence of local infection:

- Lymph nodes are non-tender, firm, or hard
- Lymph nodes are greater than 2 cm in size
- Lymph nodes are progressively enlarging
- Other features of general ill-health, fever, or weight loss
- The axillary nodes are involved (in the absence of local infection or dermatitis)
- The supraclavicular nodes are involved

C - The presence of hepatosplenomegaly requires immediate referral.

C - Shortness of breath is a symptom that can indicate chest involvement but may be confused with other conditions such as asthma. Shortness of breath in association with the above signs (see lymphadenopathy recommendation above), particularly if not responding to bronchodilators, is an indication for urgent referral.

C - A child or young person with a mediastinal or hilar mass on chest x-ray should be referred immediately.

Brain & CNS Tumours

Children 2 Years and Older and Young People

D - Persistent headache in a child or young person requires a neurological examination by the primary healthcare professional. An urgent referral should be made if the primary healthcare professional is unable to undertake an adequate examination.

C - Headache and vomiting that cause early morning waking or occur on waking are classical signs of raised intracranial pressure, and an immediate referral should be made.

D - The presence of any of the following neurological symptoms and signs should prompt urgent or immediate referral:

- New onset seizures
- Cranial nerve abnormalities
- Visual disturbances
- Gait abnormalities
- Motor or sensory signs
- Unexplained deteriorating school performance or
- Developmental milestones
- Unexplained behavioural and/or mood changes

C - A child or young person with a reduced level of consciousness requires emergency admission.

Children < 2 Years

C - In children aged younger than 2 years, any of the following symptoms may suggest a CNS tumour, and referral (as indicated below) is required.

- Immediate referral:
    - New onset seizures
    - Bulging fontanelle
    - Extensor attacks
    - Persistent vomiting
- Urgent referral:
    - Abnormal increase in head size
    - Arrest or regression of motor development
    - Altered behaviour
    - Abnormal eye movements
    - Lack of visual following
    - Poor feeding/failure to thrive
- Urgency contingent on other factors:
    - Squint

Neuroblastoma (All Ages)

The majority of children with neuroblastoma have symptoms of metastatic disease which may be general in nature (malaise, pallor, bone pain, irritability, fever, or respiratory symptoms), and may resemble those of acute leukaemia.

C (DS) - The presence of the following symptoms and signs requires investigation with full blood count (FBC):

- Persistent or unexplained bone pain (and x-ray)
- Pallor
- Fatigue
- Unexplained irritability
- Unexplained fever
- Persistent or recurrent upper respiratory tract infections
- Generalised lymphadenopathy
- Unexplained bruising

C - Other symptoms which should raise concern about neuroblastoma and prompt urgent referral include:

- Proptosis
- Unexplained back pain
- Leg weakness
- Unexplained urinary retention

C (DS) - In children or young people with symptoms that could be explained by neuroblastoma, an abdominal examination (and/or urgent abdominal ultrasound) should be undertaken, and a chest x-ray and full blood count considered. If any mass is identified, an urgent referral should be made.

C - Infants aged younger than 1 year may have localised abdominal or thoracic masses, and in infants younger than 6 months of age, there may also be rapidly progressive intra-abdominal disease. Some babies may present with skin nodules. If any such mass is identified, an immediate referral should be made.

Wilms' Tumour (All Ages)

C - Wilms' tumour most commonly presents with a painless abdominal mass. Persistent or progressive abdominal distension should prompt abdominal examination, and if a mass is found an immediate referral be made. If the child or young person is uncooperative and abdominal examination is not possible, referral for an urgent abdominal ultrasound should be considered.

C - Haematuria in a child or young person, although a rarer presentation of a Wilms' tumour, merits urgent referral.

Soft Tissue Sarcoma (All Ages)

C - A soft tissue sarcoma should be suspected and an urgent referral should be made for a child or young person with an unexplained mass at almost any site that has one or more of the following features. The mass is:

- Deep to the fascia
- Non-tender
- Progressively enlarging
- Associated with a regional lymph node that is enlarging
- >2 cm in diameter in size

C - A soft tissue mass in an unusual location may give rise to misleading local and persistent unexplained symptoms and signs, and the possibility of sarcoma should be considered. These symptoms and signs include:

- Head and neck sarcomas:
    - Proptosis
    - Persistent unexplained unilateral nasal obstruction with or without discharge and/or bleeding
    - Aural polyps/discharge
- Genitourinary tract:
    - Urinary retention
    - Scrotal swelling
    - Blood-stained vaginal discharge

Bone Sarcomas (Osteosarcoma and Ewing's Sarcoma) (All Ages)

C - Limbs are the most common site for bone tumours, especially around the knee in the case of osteosarcoma. Persistent localised bone pain and/or swelling requires an x-ray. If a bone tumour is suspected, an urgent referral should be made.

C - History of an injury should not be assumed to exclude the possibility of a bone sarcoma.

C - Rest pain, back pain, and unexplained limp may all point to a bone tumour and require discussion with a paediatrician, referral, or x-ray.

Retinoblastoma (Mostly Children Aged Under 2 Years)

C - In a child with a white pupillary reflex (leukocoria) noted by the parents, identified in photographs, or found on examination, an urgent referral should be made. The primary healthcare professional should pay careful attention to the report by a parent of noticing an odd appearance in their child's eye.

C - A child with a new squint or change in visual acuity should be referred. If cancer is suspected, referral should be urgent, but otherwise referral should be non-urgent.

C - A family history of retinoblastoma should alert the primary healthcare professional to the possibility of retinoblastoma in a child who presents with visual problems. Offspring of a parent who has had retinoblastoma, or siblings of an affected child, should undergo screening soon after birth.

Investigations

D - When cancer is suspected in children and young people, imaging is often required. This may be best performed by a paediatrician, following urgent or immediate referral by the primary healthcare professional.

C (DS) - The presence of any of the following symptoms and signs requires investigation with full blood count:

- Pallor
- Fatigue
- Irritability
- Unexplained fever
- Persistent or recurrent upper respiratory tract infections
- Generalised lymphadenopathy
- Persistent or unexplained bone pain (and x-ray)
- Unexplained bruising

Definitions:

Grades of Recommendation

A - Based directly on level I evidence

B - Based directly on level II evidence or extrapolated from level I evidence

C - Based directly on level III evidence or extrapolated from level I or level II evidence

D - Based directly on level IV evidence or extrapolated from level I, level II, or level III evidence

A (NICE) - Recommendation taken from National Institute for Health and Clinical Excellence (NICE) guideline or Technology Appraisal

GPP - Good practice points based on the clinical experience of the Guideline Development Group (GDG)

Classification of Recommendations for Studies of the Accuracy of Diagnostic Tests

A (DS) - Studies with level of evidence Ia or Ib

B (DS) - Studies with level of evidence II

C (DS) - Studies with level of evidence III

D (DS) - Based on studies with level of evidence IV

DS - Diagnostic studies

Levels of Evidence

Ia - Systematic review or meta-analysis of randomised controlled trials

Ib - At least one randomised controlled trial

IIa - At least one well-designed controlled study without randomization

IIb - At least one well-designed quasi-experimental study, such as a cohort study

III - Well-designed non-experimental descriptive studies, case-control studies, and case series

IV - Expert committee reports, opinions and/or clinical experience of respected authorities

NICE - National Institute for Health and Clinical Excellence (NICE) guidelines or Health Technology Appraisal programme

Levels of Evidence for Studies of the Accuracy of Diagnostic Tests

Ia - Systematic review (with homogeneity*) of level-1 studies**

Ib - Level-1 studies**

II - Level-2 studies***; Systematic reviews of level-2 studies

III - Level-3 studies****; Systematic reviews of level-3 studies

IV - Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research or 'first principles'.

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

**Level-1 studies are studies that use a blind comparison of the test with a validation reference standard (gold standard) in a sample of patients that reflects the population to whom the test would apply.

***Level-2 studies are studies that have only one of the following:

- Narrow population (the sample does not reflect the population to whom the test would apply)
- Use a poor reference standard (defined as that where a 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- The comparison between the test and reference standard is not blind
- Case-control studies

****Level-3 studies are studies that have at least two of three of the features listed above***

CLINICAL ALGORITHM(S)

A series of algorithms, which summarise the principal recommendations for each cancer site, are provided in the original guideline document. These give guidance on how to proceed when a patient presents with symptoms suggestive of a cancer. They are intended to be used alongside the text version of the recommendations, which should be consulted for full, detailed guidance. The following algorithms are provided:

- Lung cancer
- Upper gastrointestinal cancer
- Lower gastrointestinal cancer
- Breast cancer
- Gynaecological cancers
- Urological cancers -- prostate
- Urological cancers -- renal
- Haematological cancers
- Skin cancers
- Head and neck cancers
- Head and neck cancers -- thyroid
- Brain and central nervous system (CNS) cancers
- Brain cancers and soft-tissue sarcomas
- Children's cancers -- leukaemia and lymphoma
- Children's cancers -- brain tumours
- Children's cancers -- neuroblastoma and Wilm's tumour
- Children's' cancers -- bone tumours, sarcoma and retinoblastoma

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is provided for each recommendation (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early referral has a role to play in the improvement of care for people with cancer, and in some cancers early referral may improve survival rates.

POTENTIAL HARMS

False-positive and false-negative results of cancer diagnostic studies

QUALIFYING STATEMENTS

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- This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Many recommendations in this guideline are graded C or D. This is an inevitable consequence of the focus in the guideline on symptoms and signs rather than clinical interventions, and it would be inappropriate to infer from the grade given to most of the recommendations in this guideline that the recommendations are not important. The relevant studies have usually described the presenting symptoms and signs in patients with the cancer of interest, and some studies have compared the findings among patients who were subsequently found to either have or not have cancer. It is essential to note that the guideline group has been able to use this evidence to make recommendations it regards as highly important.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation in the National Health Service (NHS)

Resource Implications

Local health communities should review their existing practice for referral for suspected cancer against this guideline. The review should consider the resources required to implement the recommendations set out in the original guideline document and the "Major Recommendations" section of this summary, the people and processes involved, and the timeline over which full implementation is envisaged. It is in the interests of people with suspected cancer that the implementation timeline is as rapid as possible.

Relevant local clinical guidelines, care pathways, and protocols should be reviewed in the light of this guidance and revised accordingly.

General

The implementation of this guideline will build on the National Service Frameworks for NHS Cancer Plan 2000 and Older People in England and Wales and should form part of the service development plans for each local health community in England and Wales. Other key health strategies include the service improvement guides produced by the Cancer Services Collaboratives.

Audit

Suggested audit criteria based on the key priorities for implementation are listed in Appendix D of the short version of the guideline and in section 6 of the full version, and can be used to audit practice locally.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Clinical Algorithm
Patient Resources
Quick Reference Guides/Physician Guides
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer in adults and children. London (UK): Royal College of General Practitioners; 2005 Jun. 791 p. [452 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Jun

GUIDELINE DEVELOPER(S)

National Collaborating Centre for Primary Care - National Government Agency [Non-U.S.]

SOURCE(S) OF FUNDING

National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Guideline Development Group (GDG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Guideline Development Group Members: Dr Ivan Cox, General Practitioner and GDG Chairman, Birmingham, West Midlands; Dr Emily Banks, Deputy Director, Cancer Research UK, Epidemiology Unit, Oxford; Dr Kathie Bynish, Director, London Cervical Screening QA Reference Centre, Charing Cross Hospital London; Ms Ann Brown, Elderly Care Specialist Nurse, Sunderland; Ms Debbie Coats, Senior Informaton Development Nurse, CancerBacup, London; Ms Margaret Evison, Consultant Clinical Psychologist, St Thomas's Hospital, London; Dr E.D Gilby, Consultant Medical Oncologist, Royal United Hospital, Bath, Avon; Professor R. Hornung, Professor of Medical Education, University of Surrey; Dr Orest Mulka, General Practitioner, Measham, Leicestershire; Dr Robert Newton, Cancer Research UK, Cancer Epidemiology Unit, Oxford University; Mr Richard Palmer, Chairman of the National Alliance for Childhood Cancer Parent Organisations, Leicestershire - Kent; Mr N.I Ramus, Consultant Breast, Endocrine and General Surgeon, Taunton and Somerset Hospital; Ms Louise Soanes, Senior Sister (Children's Services), The Royal Marsden Hospital, Sutton, Surrey

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

All guideline development group (GDG) members made a formal "Declaration of Interests" at the start of the guideline development and provided updates throughout the development process.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Referral guidelines for suspected cancer. NICE clinical guideline. 2005 Jun. 98 p. Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Referral guidelines for suspected cancer. Quick reference guide. 2005 Jun. 30 p. Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Referral for suspected cancer - presenter slides. 2005 Jun. 34 p. Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455, ref: N0851. 11 Strand, London, WC2N 5HR.

Additionally, Audit Criteria are available in Section 6 of the original guideline document.

PATIENT RESOURCES

The following is available:

- Referral guidelines for suspected cancer. Understanding NICE guidance -- information for people with suspected cancer, their families and carers, and the public. 2005 Jun. 55 p. Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455, ref: N0852. 11 Strand, London, WC2N 5HR.

NGC STATUS

This NGC summary was completed by ECRI on January 17, 2006. The information was verified by the guideline developer on March 15, 2006.

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